



March 1, 2000

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The Breath Test Company

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By Federal Express

US Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Dockets Management Branch [HFA-305]
5630 Fishers Lane [Room 1061]
Rockville, MD 20852

Attention: Dr. Mehul Mehta at FDA / CDER

FAX: 301-480-3212

Dr. David Green at FDA / CBER

FAX: 301-827-5394

RE: Call for Comments on DRAFT GUIDANCE for Industry

DOCKET Number: 99D-5047

DATED November, 1999

Comments on:

**Pharmacokinetics in Patients with Impaired Hepatic Function:
Study Design, Data Analysis, and Impact on Dosing and Labeling**

Dear Drs. Mehta and Green:

Our comment on this Draft Guidance for Industry, Pharmacokinetics in Patients With Impaired Hepatic Function, is strong agreement with the need to define and incorporate such assessments of hepatic function in the study of new therapeutic entities. Further, hepatic function assessment and monitoring, while critical in the target patient populations who also exhibit hepatic impairment, has valuable application in other study patients or volunteers as well.

The Guidance is primarily directed to addressing study design. However, our most specific comment is not in the study design, per se, but on the recommendations of how actual hepatic capacity may be assessed prior to and through study [and ultimately, on treatment].

Five general clinical or reported methods of assessing liver function are listed in the appendix to this Draft Guidance. These are not all commercially established methods for determining liver function. Therefore, we request inclusion of a sixth method which has published history¹⁻¹⁰.

99D-5047

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Corporate Offices and Breath Test Center 618 Grassmere Park Drive Suite 20 Nashville, Tennessee 37211 Phone 615-333-6336 Fax 615-333-6202

Breath Test Center and Research Laboratory Medical Towers Building 1709 Dryden Road Suite 1513 Houston, Texas 77030 Phone 713-799-1282 Fax 713-799-8395

The hepatic P450 mixed function oxidase is a significant pathway for the oxidative disposition of drugs and other xenobiotics. Impairment of this functional capacity significantly prolongs the residence time of administered drugs and is a well-documented measure of liver disease. This capacity can be estimated from the oxidation of ^{13}C -dimethylaminoantipyrine in a Breath Test.

We suggest the inclusion of this Meretek Aminopyrine Breath Test, a non-invasive, non-radioactive breath test as a means for classification of liver impairment. The values obtained in prior clinical investigation show strong correlation with the Child-Pugh scores and range from a cumulative percent dose oxidation value in 2h of 10% in normal subjects to as low as 1% in near-terminal liver cirrhotics.¹⁻⁶ Animal and human studies have shown that the aminopyrine breath test measures the active hepatocyte mass of the liver, a functional measurement not provided by other commonly used tests.⁷⁻⁸

Because this breath test detects the effects of drug binding to the P450 system, it has an equally valuable screening function for proposed new drugs in normal subjects and we suggest that it be noted for use in this manner before and during drug administration. This diagnostic has the potential to forecast prolongation of other concurrently administered medications, such as anticoagulant therapy, as well ⁹⁻¹⁰.

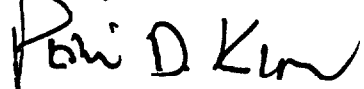
The Investigational diagnostic use of ^{13}C -aminopyrine for the assessment of hepatic function was begun under FDA review in 1972. FDA requested applications with intent for commercialization and these are under preparation for submission by Meretek Diagnostics, Inc. The non-invasive test as designed requires the collection of a baseline breath sample, the ingestion of a solution containing 500 mg ^{13}C -aminopyrine and the collection of timed post-dose breath samples.

Breath analysis by gas isotope ratio mass of the increase in $^{13}\text{CO}_2$ from an administered substrate is a diagnostic technique already commercially available (for the detection and monitoring of active *Helicobacter pylori*, Meretek UBT®).

Should there be any questions or additional information needed, please contact me by phone 713-799-1282; fax 713-799-8395; or e-mail pkleinbcm.tmc.edu.

Thank you for consideration of this comment.

Sincerely,

A handwritten signature in black ink, appearing to read "Peter D. Klein". The signature is fluid and cursive, with the first name "Peter" being more prominent.

Meretek Diagnostics, Inc.

Dr. Peter Klein
Vice President, Research and Development

Diagnostic ability of aminopyrine breath test

1. Beuers U, Jager F, Wahllander A, Ansari H, Kirsch CM. Prognostic value of the intravenous ^{14}C -aminopyrine breath test compared to the Child-Pugh score and serum bile acids in 84 cirrhotic patients. *Digestion* 1991; 50:212-218.
2. Gill RA, Goodman MW, Golfus GR, Onstad GR, Bubrick MP. Aminopyrine breath test predicts surgical risk for patients with liver disease. *Ann Surg* 1983; 198:701-704.
3. Henry DA, Kitchingman G, Langman MJ. [^{14}C]Aminopyrine breath analysis and conventional biochemical tests as predictors of survival in cirrhosis. *Dig Dis Sci* 1985; 30:813-818.
4. Monroe PS, Baker AL, Schneider JF, Krager PS, Klein PD, Schoeller D. The aminopyrine breath test and serum bile acids reflect histologic severity in chronic hepatitis. *Hepatology* 1982; 2:317-322.
5. Saunders JB, Lewis KO, Paton A. Early diagnosis of alcoholic cirrhosis by the aminopyrine breath. *Gastroenterology* 1980; 79:112-114.
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Correlation of aminopyrine breath test with active hepatocyte mass

7. Lauterburg, BH, Bircher J. Expiratory measurement of maximal aminopyrine demethylation : in vivo effect of phenobarbital, partial hepatectomy, portacaval shunt, and bile duct ligation in the rat. *J Pharmacol Exp Ther* 1976; 296: 501-505.
8. Hepner GW, Vesell ES. Assessment of aminopyrine metabolism in man by breath analysis after oral administration of ^{14}C aminopyrine. Effects of phenobarbital, disulfiram and portal cirrhosis. *N Engl J Med* 1974; 291:1384-1388

Aminopyrine breath test detection of drug effects on liver function

9. Rollinghoff W, Paumgartner G. Inhibition of drug metabolism by cimetidine in man: dependence on pretreatment microsomal liver function. *Eur J Clin Invest* 1982; 12:429-43
10. Kramer, P, McClain, CJ. Depression of aminopyrine metabolism by influenza vaccination. *N Engl J Med* 1981; 205:1262-1264

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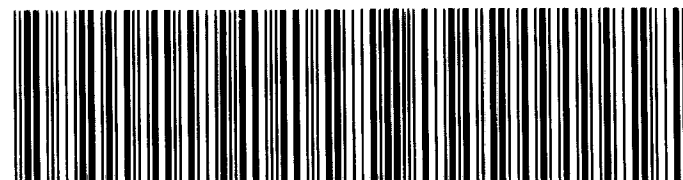
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